LSD FOLLOW-UP STUDY REPORT

OCTOBER 1980

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US ARMY HEALTH SERVICES COMMAND
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EXECUTIVE SUMMARY

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Because of its potential use as a chemical warfare agent, lysergic acid diethylamide (LSD) was utilized in a series of experiments by the Army Chemical Corps during the period from 1955 through 1967. Volunteer subjects for these experiments were solicited from the Army at large. As far as can be determined from the existing records, nearly all of the studies were carried out under strict medical supervision and written consent was obtained from the volunteers prior to the administration of LSD or any other agents although the specific agent(s) may not have been identified by name.

Several years after the termination of the LSD experiments in 1967, one of the test subjects contacted the Army with the information that he had been advised by his private physician that the recent onset of temporal lobe epilepsy in this subject might have been caused by his exposure to LSD some years before. Other subjects who received LSD in the same group as this individual were invited to enter Walter Reed Army Medical Center for a thorough medical and neuropsychiatric evaluation. In the meantime, growing public and congressional interest in chemical warfare testing was stimulated by the disclosure of the cases of Dr. Olson and Harold Blauer, among others. Although neither case was related to the chemical warfare experiments conducted by the Army from 1955 to 1967, there was enough concern to mandate the attempt to evaluate other individuals who had received LSD. Following a second brief evaluation project (Project 28) involving individuals who had previously requested examination, a pilot study (Project 50/50) was designed and completed in 1977. The results of this study were used to guide the design of a full-scale follow-up project. The full-scale project attempted to contact every individual for whom present addresses could be obtained and invite them to enter one of three Army medical centers for evaluation. The three centers involved were Walter Reed Army Medical Center in Washington, D.C., Dwight David Eisenhower Army Medical Center in Augusta, Georgia, and Letterman Army Medical Center in San Francisco, California. Subjects entered the hospital closest to their home residence and underwent a week-long series of studies including complete medical and neurological examinations, screening laboratory studies, electroencephalography, psychiatric interview, ophthalmology and ENT consultations, and a Halstead-Reitan Neuropsychological Test Battery. The data was collected by the central project office and entered into programmed forms for computer analysis.

Following completion of the data analysis, the pertinent findings were entered into a comprehensive report. For reasons discussed at length in that report it had become obvious in the early stages of the project that a control group with which to compare the LSD exposed subjects could not be obtained. For that reason it was necessary to adopt the much less satisfactory strategy of comparing the examined subjects with males in the general United States population in the same age range. On that basis, the medical illnesses found appeared to be similar with respect to frequency and type to that found in the comparable general population.

Likewise, the incidence of psychiatric illness was identical to that of the general population. As a group, the LSD exposed subjects appeared to be unusually well-educated, maritally stable, and economically successful. Specific concerns about the induction of seizure disorders by LSD exposure were determined to be unfounded. There was no consistent evidence of any chromosomal damage in those patients for whom chromosome studies were obtained, and except for a possible increase in the incidence of congenital heart disease in children born after paternal LSD exposure (which in any case did not exceed the national incidence of congenital heart disease) there was no suggestion of LSD-related damage in offspring of LSD subjects. Neuropsychological testing showed abnormalities in about one-third of the subjects but most of these abnormalities were borderline and 73% had probable etiologic explanations other than LSD exposure. Only 16% of the patients reported psychological symptoms occurring within a reasonable proximity to LSD exposure (defined as within two years) and most of these symptoms were benign and self-limited. Only 7% of the subjects interviewed felt that they had suffered any socioeconomic disablilty from their LSD exposure.

In summary, then, the majority of subjects evaluated did not appear to have sustained any significant damage from their participation in the LSD experiments; and in those cases where there were abnormalities either by history or on examination, LSD could not generally be identified conclusively as the causative agent because of the many confounding variables which could not be controlled. Chief among these were length of time having elapsed between LSD exposure and onset of symptoms, length of time having elapsed btween LSD exposure and time of examination (up to 20 years), exposure to multiple other chemicals in addition to LSD, intervening adverse life circumstances, and individual motivations for seeking examination. It must be expected that similar problems would beset any study attempting to answer similar questions about exposure to chemical agents some twenty years before so that future follow-up studies of this nature are probably inadvisable from a scientific viewpoint. Nevertheless, because some subjects seem to have legitimate complaints that might reasonably be considered to have arisen from LSD exposure, such persons should continue to be afforded the opportunity to present their complaints for consideration on a case by case basis.

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INTRODUCTION

Background

The remarkable hallucinogenic properties of lysergic acid diethylamide (LSD) were discovered, by accident, in Switzerland in 1943. It was not until the early 1950's, however, that this discovery began to make an impact in the scientific world and almost immediately thereafter spread to the general public. By coincidence, this era was also the height of the "cold war" and a time of extremely active experimentation with chemical warfare agents. At first glance, LSD seemed to possess many properties desirable in the "ideal" chemical warfare agent. It was known to be effective in incredibly small amounts and conveniently colorless, odorless, and tasteless. Because of these properties, in addition to the rumored use of LSD or some similar agent by certain Soviet bloc nations for the purpose of interrogation and behavioral control (brainwashing), the US Army Chemical Corps and the US Army Intelligence Corps decided to conduct a series of experiments with LSD. These tests were begun in 1955 and continued through 1967. Volunteer research subjects were solicited from the Army in general and from the Chemical Corps. With rare exceptions, all LSD-exposed subjects voluntarily participated in the chemical warfare testing and were informed ahead of time that they would be receiving a psychoactive agent, although the agent was not specifically identified. Strict medical supervision was provided during the testing and, prior to the actual receipt of drugs, almost all subjects received some degree of psychological screening. The bulk of the testing was carried out at Edgewood Arsenal, Maryland, although other sites were

occasionally used. Projects were designed to obtain information not only about the possible usefulness of LSD in operations against an enemy force but also about means that might be taken to defend against the use of LSD to disrupt US forces. By 1967, the necessary data had been obtained and further LSD research was discontinued.

The Preliminary LSD Follow-up Projects

Several years after the termination of LSD testing, the Army was notified that a former participant had developed temporal lobe epilepsy. This individual, along with those others who had participated in LSD testing at the same place and time, was invited to enter Walter Reed Army Medical Center (WRAMC) for a thorough medical evaluation with emphasis on neurological, psychiatric, and psychological testing. The original group of volunteer subjects numbered 34, but since one had been killed in combat in Vietnam in the interim, 33 subjects were potentially available for follow-up. Hence, the title, "Project 33."

Project 33 was carried out in 1974 and 1975. In the meantime, public and congressional interest in chemical warfare testing was stimulated by, among other things, the disclosure of the tragic suicide in 1953 of an Army mathematician shortly after surreptitiously being given LSD by non-military experimenters. In 1975, congressional investigators requested that measures be taken to locate and evaluate for possible long-term adverse effects all former participants in Army chemical warfare research with LSD.

Initially, it was thought that this might be accomplished by asking former LSD recipients who desired evaluation to contact a designated Army office. Twenty-eight individuals did so and were invited to enter Walter Reed Army Medical Center to participate in the second of the early LSD-related projects entitled "Project 28." Project 28 was similar in format to Project 33, consisting of medical, neurological, and psychiatric examinations, psychological testing (Halstead-Reitan Battery), and screening laboratory studies including EEG and chromosome analysis.

It was readily apparent, however, that a more comprehensive approach to the overall problem was needed in order to safeguard the welfare of the former chemical warfare volunteers and to satisfy public and congressional interest. To accomplish this, Walter Reed Army Institute of Research (WRAIR) was tasked to prepare a protocol for the examination of the LSD subjects and WRAMC was selected as the site of examination. At the same time, a list of all former LSD recipients was compiled. All individuals for whom a current address was available were contacted by WRAIR, informed that they had received LSD in chemical warfare experiments, and notified of the Army's intention to conduct follow-up examinations.

The efficacy of the proposed protocol was tested in a pilot study entitled "Project 50/50." This title referred to the intention of testing 50 former LSD recipients selected at random from the computer printout listing all LSD subjects from 1955 through 1967 and a matched control group of 50 non-LSD-exposed individuals selected from Army personnel records

covering the same period. The Project 50/50 protocol basically elaborated on the design of the preceding two ad hoc studies. The protocol provided for aproximately one week's hospitalization during which time the subjects received the following: a general medical examination, a separate neurological examination, and a battery of laboratory studies including a complete blood count, serum chemistries (SMAC 20), serology, urinalysis, chest film, electrocardiogram, and electroencephalogram. In addition, the subjects were asked to fill out a series of questionnaires dealing with their medical history, psychiatric history, drug and toxin exposures, current life events and opinions, and experiences with psychoactive agents. Neuropsychological evaluation was obtained through the administration of the Halstead-Reitan Battery. Finally, the subjects were seen in consultation by the Psychiatry, Ophthalmology and Otolaryngology (ENT) Services, all of which performed screening examinations.

A major and eventually insuperable problem arose with regard to the proposed study design; namely, it proved impossible to obtain matched controls for the LSD-exposed subjects. Part of the difficulty was due to the unique nature of the LSD-treated group itself. A self-selected group (by virtue of volunteering for participating in chemical warfare studies), the LSD subjects were not in any sense a random cross-section of the Army population. For example, the average intelligence and level of education of the LSD-treated group, based on AFQT (Armed Forces Qualifying Test) scores and educational history, was considerably higher than that of the Army population in general. This was due, in part, to the large proportion

of Chemical Corps and Intelligence Corps officers, many with advanced scientific degrees, in the LSD group. Furthermore, where self-selection occurs, the question of motivation becomes critical. Experience suggests that individuals of higher intelligence--and hence greater curiosity--tend to be over-represented among volunteers for research projects in general. This factor may have contributed to the observed bias toward higher intelligence.

Other factors may also be presumed to have been in operation to increase biasing in less predictable ways. Some enlisted subjects are known to have volunteered in order to avoid, if only temporarily, an unpleasant or boring work situation. Others volunteered for the tests in order to spend time in a particular geographical area nearer family, friends, or other points of personal interest. For the officers, volunteer participation was rarely an escape mechanism; on the contrary, a few reported that they would probably have declined to participate if they had not been strongly influenced to do so by perceived pressure from their superiors. Finally, since all those who volunteered knew, at the minimum, that chemical warfare agents were being tested, it would have been extraordinarily naive for them not to have assumed that they might be exposed to potentially toxic compounds. Therefore, it seems probable that so-called "risk takers"--a well-recognized subgroup in psychiatric studies--would be attracted to, and over-represented in, the volunteer population.

Since the response to LSD ingestion has been shown to be dramatically influenced by non-drug factors, selecting control subjects to neutralize

these factors has been a chronic problem in all LSD research. In their frustration, some authors have even seriously questioned the possibility of using control groups in any research on psychoactive drugs. Nevertheless, even though recognizing the numerous biasing factors described in the previous paragraphs, an attempt was made to select potential control subjects from contemporary Army personnel rosters.

Even limiting matching criteria to age, education, intelligence (AFQT) scores, and marital status, it proved extremely difficult to identify suitable control subjects. In part, this was due to the destruction of many records in the Army Records Center at St. Louis during a fire in 1967; and, in part, to the sketchiness of information in existing records.

Once basic matching criteria were satisfied, the next problem was to find current addresses for those identified as potential controls. Since Army records generally reflect only a servicemember's address immediately prior to entering the service or the address of his next of kin, present addresses were rarely available by simple inspection. Other avenues of approach, such as examining records kept by the VA system or the IRS, were severely restricted due to requirements to comply with Privacy Act regulations. After 6 months of continuous effort by a records specialist, only 30 potential control subjects had been located; of these, only 3 were willing to serve as control subjects given the necessity of spending one week in the hospital for the modest stipend offered.

Faced with these difficulties, Project 50/50 proceeded without matched controls and confined itself almost exclusively to the evaluation of LSD-treated

subjects. Eventually, six control subjects were examined including three subjects who had received other chemical warfare agents but not LSD. The pilot project was completed in the early summer of 1977, and the accumulated data from Projects 33, 28, and 50/50 were analyzed by WRAIR personnel. It appeared that the distribution of general medical illnesses within the group of the 112 LSD-treated subjects evaluated as of that time closely paralleled that which would have been expected in the general male population of the same age distribution. There was no convincing evidence of increased chromosomal damage, increased birth defects in offspring, or increased seizure frequency, all issues raised prior to the start of the study. The distribution of psychiatric illness likewise seemed to approximate that of the general population. However, the performance on the Halstead-Reitan Battery by the LSD group as a whole seemed somewhat poorer than would have been expected. No consistent direction of deviation was noted and the possibility was raised that the poorer group performance was partially artifactual due to the inclusion of a number of subjects who had contacted the follow-up with dubious complaints or had threatened litigation, or both.

A final finding served to underline the futility both of trying to find closely matched control subjects and of trying to establish any casual relationships between LSD exposure and observed abnormalities 10 to 20 years later. In the years following participation in LSD testing, a remarkable number of LSD-treated subjects became exposed through their occupations and hobbies to a great variety of other toxic agents. (See

Table 11.) Without finding controls who had been similarly exposed, any comparison of the results would have been suspect.

The results of Project 50/50 caused the abandonment of the idea of doing a classical matched control follow-up. However, there remained the necessity to obtain as much information as possible about the current status of LSD-exposed subjects. After careful consideration, the decision was made to continue with a more clinically oriented survey of as many of the LSD subjects as could be tested.

Organization of the Final LSD Follow-up Study

In 1978 the responsibility for completing the LSD Follow-up Study was given to the US Army Health Services Command (HSC). A follow-up office was established at WRAMC and the material from the preceding three studies was turned over to that office by WRAIR. Upon receiving the comprehensive roster of individuals believed to have received LSD in Army chemical warfare projects between 1955 and 1967, the new follow-up office proceeded to contact all individuals for whom current addresses were known and to invite them to participate in the final LSD follow-up. These individuals were contacted regardless of their response to the initial contact by WRAIR in 1975-76. They were briefly told of the preliminary findings of Project 50/50 and given a 60-day period in which to indicate their desire to participate in the final follow-up study. Individuals wishing to participate were assigned on a geographical basis to one of three Army medical centers: Walter Reed Army Medical Center, Washington, DC (WRAMC);

Letterman Army Medical Center (LAMC), Presidio of San Francisco, California; and Dwight David Eisenhower Army Medical Center (DDEAMC), Augusta, Georgia. Travel to and from the medical centers was provided at government expense.

Follow-up Examinations

The follow-up examinations required approximately one week's hospitalization. Subjects were admitted to the Neurology Service at the respective hospitals where they received a thorough medical and neurological examination. Routine laboratory studies obtained consisted of a complete blood count, serum chemistries (SMAC 20 or comparable battery), urinalysis, chest film, and electrocardiogram. Additional laboratory studies were obtained if indicated, either by the past history or by clinical events during hospitalization. For example, abnormal results on the screening tests were evaluated by repetition of the test in question, followed by additional definitive studies as needed. Electroencephalography with sleep enhancement was obtained for all subjects. All subjects received the Halstead-Reitan Neuropsychological Test Battery (HRNTB). Military psychology technicians specially trained by Reitan administered the tests. The results of the HRNTB were locally reviewed for gross abnormalities, then forwarded to Reitan for definitive interpretation. All subjects received a screening psychiatric interview with emphasis on possible LSD-related problems. Ophthalmology and otolaryngology (ENT) consultations were routinely obtained and other specialty services were consulted as needed.

As a matter of policy, chronic and well-recognized medical illness was not evaluated with specific diagnostic studies unless new symptoms had recently occurred or if there was a possibility of misdiagnosis. Previously unrecognized illness was evaluated as thoroughly as possible short of hazardous or invasive procedures.

Following completion of the week's hospitalization, the available medical and neuropsychiatric findings were reviewed with each subject. The necessity for further medical evaluation, if any, was discussed in detail. Final narrative summaries from each of the participating centers were forwarded to the main project office at WRAMC. Copies of these narrative summaries were then mailed to each subject along with a questionnaire requesting an evaluation of the project as well as information on the subject's reasons for deciding to participate.

In order to obtain current medical information on as many of the original LSD-treated subjects as possible, a brief Health History Questionnaire (copyright 1971, 1974 Patient Care Systems) was sent to all locatable subjects who either directly declined to participate in the study, or failed to respond to the letter of invitation within the allotted 60-day period. In addition, each subject was asked if he had ever experienced any problems which he could relate to LSD exposure and, if so, to describe briefly those problems. Subjects receiving questionnaires were also asked to state their reason(s) for declining to participate in the in-hospital portion of the follow-up.

Data Compilation

In order to attempt to standardize, so far as possible, the data reported from each of the four LSD-related projects and present a cumulative report, worksheets were prepared and filled out using information from the clinical narrative summaries from each project, supplemented where possible by additional medical records. The information from these worksheets was then entered into a data base and tabulations prepared using an IBM 360 Mod 40. In addition, cross-tabulations of selected items were furnished by Division of Biostatistics, WRAIR.

FINDINGS

Subjects Evaluated

The computer roster turned over to the final LSD Follow-up Study Office in 1978 contained the names of 741 individuals who were thought to have received LSD between 1955 and 1967. Of these 741 names, the Army was tasked with the follow-up of 686, the remaining 55 subjects being US Air Force personnel who were followed separately. At the conclusion of the final phase of the LSD Follow-up Study, 220 subjects had been examined directly, and an additional 100 had returned completed medical history questionnaires, for a total of 320 subjects or 47 per cent of the original 686 individuals identified as LSD recipients. Of the remaining 366 potential subjects, 24 were known to have died prior to the follow-up, and 193 were unlocatable. One hundred and forty-nine were locatable (based upon the return of registered letter receipts) but declined to respond to the letters of contact or to the request to fill out a medical questionaire

or both. (See Table 1.) Of the 220 subjects examined directly, 171 were examined at WRAMC, 22 at LAMC, and 27 at DDEAMC. Project 33 (1974-75) accounted for 19 subjects; and Project 28 (1975-76) for 23. Sixty-eight subjects were seen in Project 50/50 (1977), and there were 110 who participated in the final follow-up (1978-79). (See Tables 2 and 3.)

Demographic Data

The 320 subjects participating in follow-up evaluation ranged in age from 30 to 72 years, with an average age of 45 years and a median age of 44 years. All the subjects were male. Two hundred sixty-one (81%) were married--234 (73%) to their first wives. Fourteen subjects (4%) were separated and 12 (4%) divorced. Thirty-seven (12%) were still on active duty and 117 (37%) were retired military personnel. One hundred fifty-eight left the service prior to retirement. The military/civilian status of the remaining eight could not be determined from project records. At the time of the chemical warfare agent experiments, 110 (35%) were officers and 203 (64%) were enlisted men. The rank of the remaining seven subjects could not be determined. (See Table 4.)

Reported levels of formal education ranged from 7 years to 24 years. Ten subjects (0.3%) reported less than 12 years of schooling. Sixty-eight subjects (21%) received 12 years of education (high school diploma or equivalent). One hundred twenty-five subjects (40%) completed at least one year of college and 56 of these (14%) graduated with college degrees.

just that, but again, no positive confirmatory evidence was available. Since all locatable individuals appearing on the computer roster had been contacted by WRAIR in 1975-76 and advised that they had received LSD, letters were immediately sent to those subjects listed as "unknown" or "control" explaining their correct status with respect to receiving LSD.

Of the 320 subjects evaluated in the overall follow-up, 281 (88%) specifically received LSD. Single doses administered ranged from 0.4 to 75 micrograms per kilogram (28 to 5,250 micrograms, assuming an average 70 kilogram subject). The most frequent dose administered was 1.0 to 1.5 micrograms per kilogram. Subjects who received LSD were given one to five doses. One hundred seventy-six subjects (63% of those receiving LSD) received one dose. Forty-three (15%) received two doses of LSD. Twelve subjects (4%) received three doses of LSD and two subjects (0.7%) received five. The number of LSD exposures could not be determined for 48 subjects (17%). (See Tables 7 and 8.)

A serious problem with respect to subsequent data interpretation (see "Discussion") arises from the observation that 117 (37%) of the subjects evaluated in the LSD follow-up are known to have received other chemical warfare agents or drugs in addition to LSD. Fifty-one subjects received one additional exposure, 38 received two additional exposures, and 13 received three additional exposures. Nine subjects received four additional exposures, one subject received five, and five subjects

received six. The additional exposures are to a wide variety of agents ranging from glycolates, such as Ditran and BZ, to riot control agents to alcohol. The specific agents administered are listed in Table 9 and a summary of exposures is given in Table 10.

A related issue is exposure to toxic substances subsequent to and exclusive of military chemical warfare studies. At least 48 (22%) of the 220 subjects examined directly gave a history of having been exposed to toxic substances. These exposures are detailed in Table 11. In addition, 11 (12%) of the directly examined subjects admitted usage of marijuana or other illicit drugs.

Deceased Subjects

Twenty-four persons are known to have died prior to the start of the follow-up evaluations. The causes of death are known for 21 of these individuals and are as follows: heart disease (10), gunshot wound (4), cancer (2), aircraft crash (2), respiratory failure secondary to amyotrophic lateral sclerosis (1), acute alcoholic intoxication (1), and emphysema (1). Two of the four fatal gunshot wounds were sustained in combat in Vietnam. Of the remaining two, one was self-inflicted, and one occurred under unexplained circumstances. In this last instance, suicide was a possibility but there apparently was no conclusive evidence one way or the other. The death from suicide occurred 3 years after LSD exposure. The unexplained shooting death occurred 15 years after LSD exposure.

For the remaining subjects, the elapsed time from LSD exposure to the time of death ranged from 3 to 18 years with a median of 13 years and a mean of 12 years. It is possible that some of those subjects listed as unlocatable have in fact died, but there is no feasible way to obtain further information at the present time. (See Table 12.)

Medical Illnesses and Laboratory Findings in Subjects Examined

The discharge diagnoses for those 220 subjects who participated in the in-hospital portion of the LSD follow-up are given in order of frequency in Table 13. Diagnoses found in the "Past Medical History" portion of the clinical records are listed in Table 14.

For individuals returning medical history questionnaires, it was often difficult to determine the exact dates of occurrence, chronological sequence and present status of listed complaints and diagnoses. Therefore, the medical conditions of this group are listed by frequency of occurrence without distinguishing "present" from "past" illnesses. (See Table 15.)

The medical and neuropsychiatric evaluations provided to LSD follow-up subjects revealed previously unrecognized illness in 70 (32%) of the 220 subjects examined. The diagnoses ranged from trivial (e.g., asymptomatic nasal septal deformity) to potentially damaging (e.g., hypertension) to major illness (e.g., nasopharyngeal carcinoma). A complete list of the illnesses discovered is given in Table 20. Appropriate therapy was

instituted in 29 cases. In the remainder, the nature of the illness and the need, if any, for further evaluation was discussed with the subjects prior to discharge.

Since laboratory abnormalities were generally incorporated in the final diagnoses (e.g., anemia, heart block, granuloma on chest X-ray), they will not be specifically detailed with the exception of the results of electroencephalography, chromosome analysis, and the Halstead-Reitan Neuropsychological Test Battery findings.

Electroencephalography was obtained in 214 cases and was abnormal in 9 cases. The abnormalities reported were generally mild and are listed in Table 21.

Chromosome analysis was obtained in 26 cases, of which 18 showed no abnormalities. Abnormalities were found in five cases and consisted of an increased break and gap rate in one and extra chromosome groups in the remaining four cases. These latter findings were probably artifactual for reasons that will be discussed later. Of the 18 subjects whose chromosome analysis showed no abnormalities, 14 received LSD only, 3 received LSD plus another chemical warfare agent, and 1 received no drugs. All five of those cases whose chromosome studies showed abnormalities received only LSD. Three reports were pending at the time of the preparation of this paper. (See Tables 22 and 23.)

Congenital Abnormalities in Children of Subjects Evaluated

The presence of congenital and other abnormalities in the children of LSD and chemical warfare agent-exposed subjects was also investigated.

Of the 588 children born to 246 of the 320 LSD subjects evaluated, the birth order is known for 356. Of these, 155 were born before their father's exposure to LSD, and 201 were born after their father's LSD exposure. Reported abnormalities were classified as "major" if they were disfiguring or disabling or both; and as "minor" if they were neither cosmetically nor medically significant. Other abnormalities were classified as "possible" if they could conceivably have been related to paternal LSD exposure but are not generally recognized as congenital illness. Finally, abnormalities occurring in children from families with prior histories of similar defects were classified as "familial." For example, the two children with "pigeon feet" were siblings from a family with a prior history of such defects in other family members.

Using these criteria, there were five "major" and one "possible" abnormalities in the 155 children born prior to their father's LSD exposure. There were 8 "major" abnormalities in the 201 children born after paternal LSD exposure including four cases of congenital heart disease. In the same group, there was one "minor" abnormality, six "possible" abnormalities, and three "familial" abnormalities. (See Table 24.) Statistical analysis of these data is discussed below.

Halstead-Reitan Test Battery Findings

Because of the relatively brief period of time available between the conclusion of the LSD follow-up examinations and the preparation of this report, only a preliminary summary of the results of the neuropsychological

testing was available from Reitan. This preliminary summary does not include the results of the last several subjects examined; however, it seems unlikely that the results of the final few examinations will significantly alter either the results or the conclusions reached.

Combining the results of the pilot study (Project 50/50) with those of the final LSD Follow-up Study, the Halstead-Reitan Battery was given to 172 LSD-exposed subjects. For preliminary analysis, Reitan was asked to report the results based upon five possible categories: (1) normal; (2) mild or borderline impairment with no known cause; (3) mild or borderline impairment with a probable etiology; (4) abnormal with no known cause; and (5) abnormal with a probable etiology. A probable etiology was defined as a past or present medical or psychiatric condition (exclusive of LSD exposure) which, based upon prior experience, was known to have produced abnormalities similar to those found in the case in question. Of the 172 subjects tested, 95 (55%) were rated normal in performance. Fifty-five subjects (32%) exhibited mild or borderline impairment without an identified etiology. Sixteen subjects (9%) tested at the same level were found to have a probable etiology. One subject (less than 0.5%) was rated abnormal with no known etiology, and five (3%) were rated abnormal with identifiable probable etiology. For those subjects whose results fell in the mild impairment with known cause category, the identified possible causes included: head injury (14), stroke (2), multiple sclerosis (2), meningitis (2) drug abuse (1), and unspecified (1). For those five subjects fallinginto the abnormal with known etiology category, the results were attributed

to alcoholism (2), encephalitis (1), head injury (1), and metastatic cancer to the brain (1).

According to standard procedures, the history upon which the determination of possible etiology was made was obtained immediately prior to the testing by the psychology technicians administering the test battery. The subject's medical records were not necessarily reviewed as a part of this determination. Some errors may have been introduced either by overlooking existing diagnoses or, since the testing usually took place early in the course of hospitalization, by being unaware of diagnoses made subsequent to the psychological testing. To minimize these sources of error, the final charts of those subjects falling into either of the categories of impairment with no known etiology were reviewed. Of the 55 subjects who were classified as showing "mild impairment without known etiology," possible etiologies were found in 34 cases. The proposed etiologies were as follows: neurologic disorder (12), psychiatric disorder (8), alcohol abuse (8), head trauma (6), exposure to toxic chemicals (16), use of illicit drugs (4). The one subject who was found to be clearly abnormal with no known etiology had a history of hypertension and head trauma. The results of the Halstead-Reitan testing are summarized in Table 26.

Adverse Reactions

Seventy-six subjects (24%) reported one or more long-term adverse reactions from LSD exposure. These cases are listed in Table 29 and categorized as follows: "probable" LSD effect; "possible" LSD effect; "doubtful"

LSD effect; and adverse effect reported by a subject found not to have definitely received LSD. A probable LSD effect was defined as one which was reported to have initially occurred within 2 years of LSD exposure and which is either similar to known long-term effects of LSD or could conceivably have been caused by LSD even if not previously reported. A possible LSD effect met one but not both of the preceding criteria; a doubtful LSD effect met neither. The arbitrary period of 2 years was chosen because this is the generally accepted extreme limit for the onset of flashbacks, the most common delayed reaction to LSD.

Fifty subjects (16%) reported symptoms which met the broad criteria for "probable" LSD effects. Of these, the most common symptom was flashbacks, defined as the spontaneous, transient occurrence of experiences reminiscent of the symptoms evoked by LSD exposure. Twenty-four subjects in this category reported flashbacks. Symptoms ranged from replication of LSD experience to recurrent feelings of anxiety and depersonalization. Six subjects had only a single flashback. Eighteen had multiple episodes and, of these, 13 subjects reported occasional recurrences of their symptoms to the present.

The next most frequent adverse reaction in this category was depression. Nine subjects reported post-LSD depression. There was one suicide attempt, one suicide gesture, and at least two cases in which suicidal ideation occurred. In the remaining five cases, the depression was generally milder and more episodic in nature. Five subjects reported personality

changes ranging from mildly increased irritability to explosive outbursts. Four subjects reported dissociative episodes, two of which occurred only during alcohol intoxication. Other complaints in order of frequency included: anxiety (4), nightmares (3), paranoia (3), alcohol abuse (2), polydrug abuse (1), episodic withdrawal (1), acute confusional state (1), and seizure disorder (1). Somatic complaints were fairly frequent and included: headache (3), tinnitus (1), a peculiar "fizzing" noise (1), and transient impotence (1).

For the 12 subjects falling in the "possible LSD effect" category, the complaints included: depression (3), flashbacks (2), memory loss (2), "blackouts" while drinking (1), alcohol abuse (1), drug abuse (1), multiple somatic complaints (1), and "problems" with nervous system (1). For those six individuals falling in the "doubtful LSD effect" category the complaints were exclusively somatic and included: "eyes dilate a lot"; vague weakness; chronic dyspnea; stiff muscles and hot flashes; photophobia; and allergies.

The remaining eight individuals were not known to have received LSD (or any other agent in seven cases) but nevertheless presented striking complaints. The non-somatic complaints included: personality change and alcohol abuse; nightmares and social withdrawal; phobia and indecisiveness; and flashbacks, fear of insanity and death, chronic anxiety, and chronic gastric distress. Two individuals in this category had only somatic complaints: headache and inner ear problems (vertigo).

As was the case with the LSD population in general, exposures to other chemical substances complicated the findings. Thirty subjects (40%)

reporting adverse effects received one or more chemical warfare agents in addition to LSD, and one subject received only a non-LSD agent. Many of the agents administered possessed potent psychoactive properties. (See Tables 31 and 37.) In addition, 16 subjects reported exposures to toxins other than chemical warfare agents (Tables 32 and 38), 13 subjects reported exposures to illicit drugs (predominantly marijuana), and 15 reported at least some excessive use of alcohol.

An attempt was made to determine if such factors as age, rank, number of doses of LSD, and location of experimentation affected the likelihood of adverse effects being reported. There were no obvious differences between the subjects reporting adverse effects and the LSD follow-up group as a whole with respect to present age or age at time of exposure and number of doses of LSD administered (Tables 33, 34, 35, 36). A small increase in the percentage of enlisted men in the group reporting adverse effects compared with the percentage of enlisted men in the total population was noted and proportionately slightly more adverse effects occurred at Edgewood Arsenal than at other sites. Since almost all officers participated in LSD testing at either Fort McClellan or Fort Benning, the observed difference in reported adverse effects, if significant, might be due to either differences in testing procedures at different locations or to differences in the response of enlisted men compared with officers or both.

Motivation for Participation

Since only 47 per cent of the 469 locatable LSD-exposed subjects consented to enter the in-hospital phase of the LSD follow-up, an attempt was

made to determine the motivation(s) of this group. The two most frequently cited reasons for participation were a desire for a complete medical check-up (54%) and concern about possible long-term LSD effects (52%). Other reasons given included: desire to assist the Army (29%); specific concerns with respect to health (7%); and other (12%). (See Table 27.)

Those subjects who declined to participate in the in-hospital phase of the LSD study were also asked to state their reasons. Lack of available time (56%) and loss of income (10%) were cited as well as lack of concern about possible long-term LSD effects (36%). Distrust of Army motives was cited by 8% and other reasons given by 20%. (See Table 28.)

DISCUSSION OF FINDINGS AND OBSERVATIONS

"A wise man proportions his belief to the evidence."

-David Hume, 1711-1776.

Review of Recognizable Limitations to Data Interpretation

Prior to embarking on a discussion of the results of the LSD Follow-up Study, those factors which can be recognized to introduce both theoretical and practical limitations to the data interpretation will be reviwed briefly. As described at length previously, the original LSD-exposed population was not a random sample of the general Army population because of multiple biasing factors operating prior to LSD exposure. Furthermore, since medical follow-up information was obtained on only 320 subjects (47% of the original 686 LSD recipients and 64% of the 496 LSD recipients

currently locatable), the data are incomplete. The question of motivation for those who did elect to participate then becomes crucial. The results of inquiry into the motivation for either participating or not in the follow-up study showed, as expected, that many (54%) of those who declined the offer of a follow-up evaluation did so because they were not willing to take the necessary time. This suggests that these individuals as a group had relatively fewer serious health concerns and/or concerns about possible long-term LSD complications than did those subjects participating in the in-hospital follow-up--for whom desire for a thorough medical examination and concern about LSD effects were the most frequently reported motivating factors. However, there was no significant difference in the frequency of reported LSD-related problems: 22 per cent (n=22) for those responding by questionnaires versus 25 per cent (n=54) for those actually examined. A few of those reporting long-term LSD effects refused to be examined in person out of suspicion of Army motives.

The inability to obtain a matched control group has been discussed. However, even if satisfactory controls could have been found by reviewing information in the existing personnel records of the period from 1955-1967, it would have been clearly impossible to assure continued matching with respect to intervening life experiences, including exposure to other toxins, during the 9- to 24-year period from the time of LSD exposure to the time of participation in the LSD follow-up (mean, 19 years).

Another problem with no known means of resolution was the administration of other chemical warfare agents besides LSD to the LSD-exposed subjects.

According to Edgewood Arsenal records, 117 (36.5% of the total LSD study group) received one or more additional exposures to other chemical warfare agents. Forty-one per cent of those subjects reporting "LSD-related" complications received other chemical warfare agents in addition to LSD. As previously noted, the reciprocal of this problem also exists. Many of the names on the computer roster are listed as having received an "unknown agent" or being "controls." Of the 76 individuals reporting LSD-related complications, 7 fall in the "unknown agent" category or in the "control" category.

Final confounding factors may be found in physician performance and in the interaction between the examining physicians and the follow-up subjects. In the period 1974 through 1979 at least 100 different physicians have examined these LSD follow-up subjects. Of these there have been at least 20 "primary physicians"--defined as the physician dictating the final narrative summary. The author of this report was the "primary physician" for the greatest number of subjects (n=68). Each of the remaining "primary physicians" typically were responsible for 2 to 20 subjects. In each of the four component phases of the LSD Follow-up Study careful instructions and background briefings were given in an attempt to standardize the evaluations so far as possible. However, because of the intense controversy surrounding the LSD Follow-up Study, and in particular the concern on the part of many physicians about future litigation, there was inevitably some variation in physician performance as reflected in some consistent differences in the report findings among the three participating centers.

There was also evidence of variable effort and cooperation on the part of some test subjects. Some subjects appeared to be attempting to minimize their complaints while others, not infrequently in connection with obvious personal gain, appeared to be overstating their problems. Fortunately, both aberrations were reasonably rare.

It will be noted that although there are many numerical tables, there has been, with the exception of the data on birth defects, no attempt at present to apply the methods of formal statistical analysis. This is the result of the recognition of the many unknowns and uncertainties in the data and is an attempt to avoid giving the imprimatur of mathematically precise analysis where, because of the adverse conditions under which the data were obtained, such methodology is inappropriate and potentially misleading.

General Medical Findings

It has been estimated that 1 to 2 million persons[55] or 1 in 20 Americans over the age of 12[68] have used LSD or other hallucinogens. Despite such widespread usage, there are no medical conditions consistently associated with LSD exposure, although some toxic effects may rarely occur. (See below.) Therefore, it was not surprising that the general medical findings of the LSD follow-up subjects appeared to be similar in type and frequency to those expected to be found in the general male population of the United States within a comparable age range, supporting the preliminary conclusion of the pilot study, Project 50/50. Since no matched control

group is available for comparison, however, it is difficult to be very precise about the observed frequencies of particular conditions. A very rough comparison between the LSD subjects and the general US population may be made by comparing Tables 13, 14, and 15 with Tables 16 and 17. However, one must be chary of any conclusion based upon such a comparison. *Tables 16 and 17 do not specify age distributions, include both males and* females, and do not--not unexpectedly--specify military service. The LSD subjects were exclusively male, ranged in age from 30 to 72 with an average age of 45 years, and all had at least 2 years of military service. These factors must be assumed to have altered somewhat the diagnoses expected to be found among the LSD subjects. For example, malaria, an extremely rare disease in the modern United States, was reported in 12 (4%) of the LSD subjects. It can be reasonably concluded that military service introduces a greater than usual risk of contracting malaria, undoubtedly because servicemembers often serve overseas in areas of high malaria *prevalence. This example demonstrates the potential for error in attri-* buting the presence of a specific medical illness occurring with unexpectedly high frequency in the LSD study group to LSD exposure. Clearly, there can be no causative relationship between LSD exposure and malaria even though both occurred in the same group.

A similar caution must be applied to the consideration of psychiatric illness within the LSD study group. Statistics for psychiatric illness in the United States are not as well established as for general medical illness. However, recent estimates suggest that 20% of the population of

the United States suffers from functional (psychogenic) illness.[26] Estimates for specific illnesses are: schizophrenia, 0.5 to 3 per cent; manic-depressive psychosis, 0.3 per cent; neurosis including depression, 8.0 to 13.0 per cent; and personality disorder, 7.0 per cent. (See Tables 18 and 19.) These figures somewhat complicate the interpretation of the presence of psychiatric illness in the LSD subjects. If the 320 subjects evaluated could be assumed to be a random sample of the US population--which, as has been discussed, they cannot--then it would be expected that 64 (20%) would have diagnosable psychiatric illness. In actual fact, psychiatric diagnoses (excluding alcohol abuse) were made in 61 (19%) of the LSD study subjects.

With the foregoing background, only two medical/psychiatric conditions--hearing loss and alcohol abuse--will be discussed specifically, the first because of its high frequency in the LSD-exposed group and the second because it was found relatively frequently (27 subjects, or 8% of the study group) and was attributed to LSD exposure by four subjects. Hearing loss not only was the most frequent medical finding among the study subjects (88 subjects, or 28%) but also is the most common physical impairment and third most common diagnosis in the general population. The type of hearing loss found among the LSD subjects was almost exclusively that associated with chronic noise exposure. This variety of hearing loss is particularly prevalent in the military, being found in 20-30 per cent of all personnel with two or more years of service in the combat arms branches and more than 50 per cent of those with 15 or more years of

service.[86] Since LSD is not known to be ototoxic,[22] it seems reasonable to conclude that this finding should not be attributed to LSD exposure.

Alcohol abuse is also widely prevalent in the United States. It is estimated that 20 million Americans have had alcohol-related problems at some time in their lives, that 10 million have had recent problems, and that at least 1 million individuals are under treatment for alcoholism.[26] These latter 1 million individuals are largely concentrated in the 35- to 55-year age range, comparable to that of the LSD subjects. Probably the most thoroughly investigated early therapeutic use of LSD was in the treatment of alcoholism.[1,42,46,49,61,71,72,76,77] Although many of the earlier reports proved to be overly optimistic with respect to LSD's supposed benefit in the treatment of alcoholism, there were no reports of marked increase in drinking following LSD ingestion. Likewise, there are no reports known to the author in which non-drinkers have become drinkers following LSD exposure. However, in view of the four reports from the LSD study subjects (only three of which received LSD), at least a contributory relationship cannot be entirely discounted.

Halstead-Reitan Test Battery Findings

In only a few instances have LSD users been evaluated by the Halstead-Reitan Battery, but in these instances the results have been relatively consistent. The earliest reported study is that of McGothlin and others (1969). Using 16 LSD-treated subjects and 16 matched controls, these authors administered portions (sub-tests) of the Halstead-Reitan neuropsychological battery that had been previously suggested by Cohen and Edwards[20]--

although the results had not been formally published at the time--to differentiate LSD users from non-LSD users. At the conclusion of the study, only the Category Test, a test of abstract reasoning, yielded a significant difference between the two groups. Although the LSD-treated subjects did more poorly on the Trail Making A and a spatial orientation test, the differences did not reach statistical significance as in the study of Cohen and Edwards. Moreover, in this latter study, the Category Test did not show statistically significant differences between LSD and non-LSD subjects. Overall, McGothlin and his coworkers concluded that there was "no generalized evidence of organicity in the LSD group." In 1972, Wright and Hogan tested 20 repeated LSD users (mean number of exposures: 29.3 per subject) and 20 matched controls. No significant difference was found between the two groups. The following year, however, Acord and Barker[3] reported the results of the examination of 15 LSD-exposed subjects and 15 controls (the "majority" of whom had used marijuana) with portions of the Halstead-Reitan Battery. They found significant differences on two of the three tests--the Category Test and the Tactile Performance Test--and suggestive but not statistically significant differences on Trail Making B. Finally, Culver and King[23] have recently found Trail Making A abnormalities in mixed LSD and marijuana users.

In his preliminary analysis of the results of the present study, Reitan commented that an unusually high percentage of the subjects tested showed evidence of neuropsychological deficit without a demonstrable cause.

However, as has been seen, the methodology employed in determining the presence of antecedent CNS insults resulted in a number of potentially significant illnesses being overlooked. Whatever the etiology, however, these individuals showed evidence of "chronic static impairment," rather than progressive disease. The type of impairment suggested mild generalized versus focal brain dysfunction. Reitan also noted that the impairment "was not of the type that would suggest the presence of a specific *neurological diagnosis nor even of positive findings on the physical* neurological examination." Likewise, the deficits noted "would not have any serious effect (or in many instances, any necessary effect at all) on occupational capacities or in other activities in everyday living." The issue of comparison of the present results to those of the previously cited studies was not addressed in this preliminary analysis.

While there is no doubt that the Halstead-Reitan Neuropsychological Battery is an exceptionally sensitive diagnostic tool which is particularly useful in the detection and localization of subtle cerebral dysfunction, there are some additional theoretical limitations to its use which must be considered. First, Watson and co-workers[87] found that the Halstead-Reitan Battery was unable to distinguish a group of 25 "organic" neuropsychiatric patients from a group of 24 schizophrenics. Commenting on this study, Smith[77] suggests that "since patients with underlying emotional disorders may present symptoms suggestive of neurological disease, caution should be exercised when using the Halstead-Reitan Battery for diagnosis *of such patients...."* Although the results of the Minnesota Multiphasic

Personality Inventory (MMPI) were considered in interpreting the results for each test subject, it is possible that the large percentage of subjects falling within the category of mild impairment without obvious etiology may reflect the inclusion in that category of some subjects with underlying emotional disorders rather than organic brain dysfunction. If this was in fact the case, it would be expected that this category would be relatively larger in the pilot study (Project 50/50) than in the final Follow-up Study because of the inclusion by deliberate design of a number of subjects in Project 50/50 who exhibited overt emotional abnormalities. Separating the results of the Halstead-Reitan test batteries for the two phases of the follow-up project shows that 42 per cent of test subjects in Project 50/50 fell within the category of mild impairment with no known etiology, whereas only 25 per cent of the final follow-up subjects fell within this category (as reported by Reitan). Whether the proposed explanation for this observed difference is the correct one remains to be determined. However, by extension of this line of reasoning to the overall project results, it might be argued that the "unusually high" percentage of patients falling in the category of mild impairment with no known etiology might reflect an underlying emotional disorder rather than organicity. Individuals with unstable personalities prior to exposure are likely to have the most traumatic reaction to LSD ingestion and may have been relatively over-represented in this follow-up series.

Toxicity (Acute)

Although massive overdoses of LSD have produced coma, hyperthermia, tachycardia and respiratory depression[43] and possibly death,[34] the doses

used in experimental studies and medically supervised psychotherapy are not ordinarily associated with serious acute toxicity with the exception of the rare occurrence of seizures.[12,37] No deaths due to toxic overdosage have ever been reported from either experimental research or medically supervised psychotherapy. In fact, the theoretical LD50 (the dose which would be lethal to 50 per cent of humans given it) can only be approximated by comparing lethal doses for various sizes of mammals ranging from a mouse to an elephant. Extrapolating from these results (46,000 micrograms per kilogram for the mouse versus 150 micrograms per kilogram for the elephant), Hoffer[37] estimates that the theoretical lethal dose for a man is 200 micrograms per kilogram, or about 14,000 micrograms, assuming the average man is about 70 kilograms in weight. However, this estimate may well be in error since Hoffer also notes that some subjects have safely received 70,000 micrograms. The highest single dose known to have been administered to Army volunteers was approximately 5,250 micrograms.

Although seizures are sometimes considered a toxic effect of LSD, they occur quite rarely. As of 1971, only eight cases had been reported in which seizures have apparently resulted from LSD administration.[6,28] These seizures occurred exclusively in the period during or immediately after LSD exposure. For example, the subject reported by Fisher and Ungerleider (1967) experienced grand mal seizure approximately 50 minutes after LSD ingestion. Despite the occurrence, he took LSD on five more occasions and did not have another seizure until the fifth and last LSD ingestion. Early experimental studies by Monroe and Heath and associates

using electrodes implanted deeply in the brains of human subjects demonstrated the occurrence of spiking (epileptiform) activity in portions of the limbic system (hippocampus, amygadala and septal area) in response to LSD administration.[63] Experiments using scalp electrodes to record cortical activity have showed minimal and non-specific changes.[32] The relationship, if any, of these experimental findings to the epileptogenic potential of LSD is uncertain.

The report of the development of mixed grand mal and psychomotor seizures in an LSD recipient played a significant role in launching the LSD Follow-up Study. Therefore, considerable attention was given to screening for the presence of further cases of seizure disorders. In addition to the case mentioned, two other subjects were found to have a history suggestive of a seizure disorder. In the initial case, the subject had his initial seizure 1 year after LSD exposure. Although the initial fit was a grand mal seizure, the subject subsequently developed a mixed grand mal and psychomotor disorder which, for a time, proved difficult to control. Neurological evaluation at the time of the onset of seizures was non-diagnostic although an electroencephalographic abnormality was noted over the area of the right temporal lobe. This and other studies suggested a structural lesion in the same area. Neurological, neuroradiological (computerized tomography and radionucleoide brain scan), and electroencephalographic evaluation obtained by the LSD Follow-up Study 14 years later was completely normal.

The second subject gave a history of three episodes of unexplained loss of consciousness between 1969 and the present. He also reported a prolonged period of unconsciousness associated with an acute febrile illness of unknown etiology (viral meningitis or encephalitis?) in 1963. Depending upon whether or not these episodes are related, his symptoms began either 3 or 9 years following LSD exposure. Because of the finding of an abnormal EEG during the LSD follow-up, this subject was placed on anti-convulsants. A third subject also gave a history of transient alterations of consciousness that were suggestive of psychomotor seizures. However, these episodes occurred only within the first 12 months of LSD exposure and were probably "flashbacks."

In contrast to the reports in the literature, in the present study none of the subjects developing seizures or seizure-like symptoms did so during or immediately (within hours) after LSD administration. Therefore, a toxic effect of LSD may probably be excluded since LSD is essentially removed from the body 24 hours after ingestion. The diagnostic findings and the clinical course of the subject who developed seizures 12 months after LSD seem to suggest a focal lesion, such as an inflammatory process or a vascular insult, which slowly resolved leaving in its wake a seizure disorder which persisted for several years. Because of the location of the presumed lesion in the right temporal lobe, the corroborating clinical signs of structural damage may well have been subtle enough to have escaped detection during the initial evaluation. This subject's family history is pertinent in that one uncle has post-traumatic epilepsy, a

condition recently demonstrated to depend, at least in part, upon an inherited susceptibility.[13]

The second subject first developed seizure-like symptoms (paroxysmal loss of consciousness) in the setting of an acute febrile illness 3 years after LSD exposure. In this second case, the clinical features again do not seem compatible with a direct toxic effect of LSD. However, in neither case can a possible contributory or facilitory (via alteration of seizure thresholds) effect of LSD exposure be completely excluded.

Interestingly enough, there was one subject in the present study with a known chronic seizure disorder prior to LSD ingestion. He experienced no adverse effects of any sort, supporting Malleson's (1971) observation that in England a number of epileptics had been treated with LSD with no untoward effects.

Toxicity (Chronic)

The most widely discussed possible toxic effect of LSD is chromosome damage. The report in 1967 by Cohen and colleagues[15] that LSD might cause such damage sparked a storm of controversy. These researchers found increased numbers of breaks in leukocyte cultures to which LSD was added compared to control cultures. In the same report, these workers described similar abnormalities in the chromosomes of a paranoid schizophrenic treated with LSD for 4 years. Although another report in the same year supported the in vitro (cell culture) findings,[40] several other studies soon appeared which demonstrated no difference in the frequency of

chromosome breakage between LSD users and non-users.[8,48] In 1969, Tijo and co-workers[82] reported a double blind evaluation of chromosome breakage rates pre- and post-LSD exposure. No evidence of LSD-related damage was found. More recent studies[64,79] and a survey of current literature[47] have tended to support the view that LSD causes no demonstrable chromosome damage *in vivo* and may or may not cause such damage *in vitro*. In the present LSD follow-up, chromosome analysis was obtained in such a small fraction of the LSD-exposed group that it is impossible to make any type of a meaningful analysis. The increased break and gap rate found in one of the 26 cases reported is not specific for LSD and occurs "normally" in up to 5 per cent of chromosome studies. The other abnormalities cited are generally considered to be artifactual when they occur in an individual free of the stigmata of congenital malformations, as was the case in each of the four subjects listed.

A related issue is that of congenital defects occurring in children of individuals exposed to LSD. Although there are reports of congenital malformations--particularly CNS, ocular, and limb deformities--occurring in children whose mothers ingested LSD during pregnancy,[4,14,39,41,47,58] there is only one case reported of a congenital defect--a myelomeningocele--in a child whose father alone was exposed to LSD.[41]

Using classification criteria which have subsequently been adapted for use in the present study, Marden and associates[52] found major congenital abnormalities in 2 per cent and minor abnormalities in 14.7 per cent of 4,412 babies examined by external inspection only. Congenital heart

disease, which is not usually detectable solely by external inspection, is the most common "internal" congenital malformation in the United States, occurring in 1 per cent of all live births.[66] Combining these figures gives at least a 3 per cent incidence of major congenital defects in the US population. In earlier large series the percentage of major abnormalities has ranged from 2.3 to 7.5 per cent of all births with the higher figure coming from a study which extended the period of follow-up to 5 years after birth.[60] (NOTE: In the present study the children have in effect been followed from the time of birth defects to their present age.) Using 3 per cent as a conservative base rate for birth defects, no significant difference was found between the frequency of major abnormalities in the total group of 356 children born to LSD subjects and the general population. Likewise, there was no significant difference comparing either the group of children born before or after paternal LSD exposure with the general population.

With respect to congenital heart disease, however, the results are less clear. Congenital heart disease was the most common type of major abnormality noted in the post-paternal LSD group. Although there was no significant difference in the overall frequency of major abnormalities between the pre- and post-paternal LSD groups, when congenital heart disease was considered separately there was a significant increase in frequency in the post-LSD group. Nevertheless, the frequency of congenital heart disease in the post-paternal LSD group was not statistically different from that of the general population. Therefore, the

observed rise in congenital heart disease in the post-paternal LSD group may or may not be significant depending upon whether or not the population of LSD subjects in general differs significantly in a genetic sense from a sample drawn at random from the general population. Since the same fathers were in many cases represented in both groups and since major congenital abnormalities should have prevented the enlistment or commissioning of Army LSD subjects in the first place, it would seem likely that the LSD subjects are not genetically representative of the general population. In a recent survey of the possible teratogenicity of LSD, Long (1972) found no reports of congenital heart disease in offspring of LSD users although 16 of the 161 children had congenital defects.

Minor abnormalities are considerably under-represented in both the pre- and post-paternal LSD groups compared with the general population. This probably represents under-reporting due to the insignificant nature of the defects.

All statistical comparisons cited above were made using simple two-way tables and chi square. Chi square values for all of the comparisons may be found in Table 25.

A final potential result of LSD-induced chromosome damage--if any--would be the production of leukemia and related disorders. Although this has been theoretically proposed,[33] only four possible cases have ever been reported and in each of these the association may have only been fortuitous. No cases of leukemia or lymphoproliferative disease were reported by the LSD study subjects.

Finally, it has been suggested that LSD, in common with other ergot derivatives such as methysergide (Sansert), might cause retroperitoneal fibrosis. Two cases have been reported[5] in which LSD users subsequently developed this disorder but, as with leukemia, the relationship is not clearly causative nor was this disease found among the follow-up population.

Adverse Effects Reported by LSD Study Subjects

The existing medical literature concerning prolonged adverse psychological reactions--as opposed to physical toxicity--to LSD ingestion is extremely confusing with often widely disparate claims having been made concerning the hazards, or lack of same, attendant on LSD usage. Part of the problem lies with the unpredictable nature of LSD itself, part with the number of extra-drug determinants which are involved in any individual's response to LSD, and part with the intermixture of medical with social and political issues. The first of these has made it difficult to determine the exact frequency of adverse reactions, the second has hampered efforts to distinguish between LSD and non-LSD effects, and the third has effectively curtailed further responsible scientific research in the area of psychedelic drugs. With respect to the second of the above factors, Mogar (1968) has cogently commented:

> ...it has become apparent that major psychological or behavioral effects, both during and subsequent to the LSD-induced state, are not drug-specific. The nature, intensity, content and aftermath of the experience are the resultants of complex transactions between the patient's past history and personality, the expectancies of both subject and administrator, and the physical and psychological setting in which the experience takes place.

Dramatic demonstrations of this are provided by a report of paralysis following intravenous injection of normal saline into a subject who believed she was receiving LSD, and the production of flashbacks by the administration of either placebo or ephedrine sulfate to groups of subjects, including former LSD users, who were told to expect such phenomena to occur.[36]

There are basically three settings in which LSD is administered: unsupervised or "street" usage, psychotherapy and research with psychiatric patients, and medical research with normal subjects. Each of these circumstances would be expected to influence the drug response in somewhat different ways. The greatest number of prolonged adverse reactions are said to occur in "street" usage.[35,59] Part of this may be the result of the presence of more underlying or pre-existent psychopathology among street users, part may be attributable to the unstable setting in which such usage occurs, and part may be due to a tendency of many relevant medical reports to focus on adverse reactions as the basis of surveys and case reports.[50]

While reports based largely on street usage help delineate the types of adverse reactions that may result from LSD use, they are of limited value in analyzing the results of the present LSD follow-up. The setting in which Army volunteers were administered LSD was generally one of medically supervised research on normal subjects. Reports of the frequency of adverse reactions from comparable settings in the civilian community

range from "none" to perhaps 30 per cent. Some of this variation is due to different definitions of "adverse effects." Some physicians have stated that any effect of LSD is an adverse effect while others have reserved that term for only those effects which they adjudge to have been specifically harmful to the patient's overall functioning. For example, "flashbacks" could be either adverse effects or not depending upon what impact--if any--they had on the patient's well-being. (See references 9, 16, 19, 25, 29, 51, 55, 67, 73, 75, 83, 84, and 85.)

Probably the most thoroughly documented studies of the long-term effects of LSD on normal subjects have been those of McGlothlin and co-workers.[55,56,57] In 1967 they reported the results of administration of three doses of 200 micrograms of LSD to 24 carefully screened normal subjects. For comparison, control groups of 24 subjects each were given either 20 milligrams of amphetamine or 25 micrograms of LSD, presumably an ineffective dose. At 2-week and 6-month follow-ups, the LSD-treated group in general was said to show a "less defensive" attitude, more introspection, and a more passive orientation. At the 6 months' visit some lasting change was reported by 58 per cent of the LSD-treated subjects. This study limited its interest to psychological effects manifested by personality alterations. However, in 1971 McGlothlin and co-workers examined all types of LSD complications occurring in 247 individuals *receiving LSD, either for experimental or therapeutic purposes,* from 1955-1961. Those subjects were interviewed 3 to 9 years after their last LSD exposure. Twenty three per cent of the total group reported

additional non-medical LSD exposures following their participation in the supervised studies. One hundred and twenty-four subjects received LSD therapeutically, and one hundred and twenty-three were normal research subjects described as "typically well above average in educational socio-economic status." Patients in therapy typically received 3 doses averaging 125 micrograms. Experimental subjects averaged 12 doses of 125 micrograms. Both groups frequently reported more self-awareness, more tolerance, less materialism, less egocentricity and enhanced aesthetic sensibilities. Adverse reactions included flashbacks, undesirable personality changes (anxiety; depression), and somatic complaints (paresthesias; diminished eyesight), marital conflict, painful memories, loss of discipline, memory difficulties (not confirmed by specific testing), and a conviction in one case that the subject was better off without the knowledge of "escape to another world." Flashbacks, the most commonly reported adverse effect, occurred in 19 per cent of the non-medical and 13 per cent of the medical exposures. Twelve per cent of the non-therapeutic subjects felt they they had been "harmed" by their exposures to LSD compared to 9 per cent of the therapeutic subjects.

Other reports have not always clearly distinguished between prolonged adverse reactions occurring in normal subjects versus psychiatric patients. However, one can obtain a general idea of the frequency of such adverse reactions in medically supervised studies by considering the following reports. Bhattacharya (1966) reported no cases either of psychosis or of suicide attempts in 581 receiving 2,742 treatments. Malleson (1971)

surveyed 30 physicians who had administered LSD to 4,470 subjects, including 170 normal volunteers. There were 37 cases of psychosis, with 10 being permanent. There were 3 suicides, 9 suicide attempts and 11 possible attempts. All of the psychoses and all of the successful suicides occurred in the patient group. Pahnke and co-workers (1970) reported treating "over 300 patients" between 1963 and 1970 without a single case of long-term psychological or physical harm directly attributable to LSD, although there were two cases of transient disturbances. Freedman (1968) believes that in the hands of "skilled therapists" the administration of LSD should be associated with 1 per cent or less "unexpectedly traumatic" outcomes.

For the purpose of the present study, any and all complaints which LSD study subjects related in any way to their prior LSD exposure have been listed as "adverse effects." The information thus obtained, however, *is largely dependent upon the memories of the LSD subjects for events* occurring 10 to 20 years earlier with the result that at least two distortions of the data are possible. First, subjects may fail to remember brief, transient disturbances which were related to prior LSD ingestion resulting in under-reporting of such effects. Second, as has been pointed out by Cohen[19] and others,[46] the LSD experience is usually one of the most dramatic an individual will ever encounter and because of the vividness of the experience, many subsequent events, including medical/psychiatric symptoms, will tend to be attributed to LSD when in fact there is no causal relationship. Furthermore, because of the notoriety attained by Army LSD

research and the possibility of lucrative litigation, some subjects may have consciously or subconsciously altered and manipulated their complaints for their own purposes, notably self-enrichment. Of course, the reverse is also possible; i.e., that other subjects may have denied real problems in an attempt to "protect" the Army. Since there is no definitive means of detecting and compensating for these factors, it has been assumed that all the evaluated subjects were acting in good faith and their symptoms and complaints have been accepted at face value.

In the present study, 76 (24%) of the subjects reported one or more adverse effects from LSD exposure and 41 (13%) related continuation of those effects to the present time.

A. Flashbacks

Flashbacks are the best known and perhaps the most dramatic of the prolonged adverse reactions resulting from LSD ingestion. Although there is no uniform definition of the flashback experience, Cohen--who introduced the term--described flashbacks as "the spontaneous reappearance of certain effects that were experienced while under the influence of a drug like lysergic acid diethylamide (LSD)."[18] The sensations evoked may involve any of the senses--although vision is most commonly affected--and may also include complex feelings of deja vu, distortion of reality, depersonalization, anxiety, sadness, and others. As implied by this definition, flashbacks are not unique to LSD use but also occur following exposure to many other psychoactive agents, including marijuana, mescaline, STP, peyote,

and morning glory seeds.[18,80] The mechanism by which flashbacks are produced remains largely a mystery although there is no shortage of theories. Cohen believes that flashbacks are due to "behavior learned during a state of psychological arousal that can later be precipitated under conditions of nervous system arousal." Horowitz (1969) discussed other psychological theories including; (1) the "release theory" which postulated neurophysiologic changes leading to the release of normally suppressed imagery; (2) the "deconditioning theory" which suggests that during the LSD experience the individual becomes aware of certain subjective sensations to which he subsequently becomes sensitized and cannot thereafter ignore as he might have prior to LSD; and (3) the "psychodynamic theory" which states that recurrence of LSD imagery represents an attempt by the individual to "work through" the psychic material thus symbolized. Whatever the mechanism or mechanisms which trigger flashbacks, they seem to occur in about 20 per cent of LSD users.[10,55,80] Both repeated LSD ingestion and adverse reactions to LSD seem to increase the likelihood of flashbacks occurring.[18,55] Most flashbacks are self-limited and tend to be rather benign. Considered from the standpoint of adverse reactions requiring medical attention, flashbacks are rather rare, constituting only 5 per cent of the reported adverse reactions in one widely quoted series.[75] Naditch and Fenwick (1977) have reported that 57 per cent of their subjects with flashbacks described the sensations as pleasant, and 64 per cent did not find them disruptive of their daily activities. Matefy (1973) and Matefy and Krall (1974) have also commented on the relatively benign nature of flashbacks.

Of the 320 LSD subjects evaluated, 27 (8%) reported flashbacks. In 24 of the 27 cases the onset of flashbacks was within 2 years of LSD exposure. Of those two cases whose onset of symptoms exceeded 2 years from the time of LSD exposure, one subject reported a single spontaneous episode of "good feelings" reminiscent of the LSD experience 10 years after LSD exposure, while the other subject reported spontaneous episodes of feelings of "unconcern" beginning 3 years after LSD exposure and reoccurring occasionally over the next 10 years. One additional subject reported innumerable visual hallucinations associated with fear of death and fear of insanity. Although this individual's symptoms began within 1 year of his participation in chemical warfare studies, it is not known what agent he received. Most of the subjects reporting flashbacks (13, or 48%) received only 1 dose of LSD. Three subjects with flashbacks received 2 doses, and one received 3 doses. The number of doses received was unknown for the remaining nine subjects and, as mentioned, it is not known which agent, if any, one subject received.

The characteristics of the flashbacks reported were generally similar to those reported in the literature. However, there were some noticeable differences. The flashbacks were solitary in 6 cases and multiple in the remaining 21. In this series, in contrast to many prior studies, complex experiential sensations--such as feelings of well-being, jamais vu, deja vu, apprehension, unreality, and depersonalization--seemed to occur more commonly than sensory distortions and hallucinations. The most striking feature of the flashbacks reported was their unusual persistence. Eleven

subjects maintained that their flashback experiences had persisted to the present time, averaging 18 years after LSD exposure. If true, this finding is unique to this group of subjects. Although the information in the literature is sketchy, the generally accepted upper limit for the duration of flashbacks is about 2 years from the date of last exposure to LSD.[18,27] There is no immediately obvious explanation for the finding of such unusual prolongation of symptoms in the present study population. Saidel and Babineau (1976) recently reported a case of prolonged occurrence of flashbacks in which there was evidence that the symptoms were part of a conversion reaction.

Another interesting finding within this group was the occurrence of flashbacks in two cases while the individuals were in Vietnam. According to some theories, flashbacks can be precipitated by stress. In 1972, Stanton and Bardon[80] surveyed American soldiers arriving in and departing from Vietnam. They found that exposure to combat conditions had no statistically significant effect on the occurrence of flashbacks in users of hallucinogens. However, outgoing users reported a slightly higher incidence of flashbacks than incoming users.

B. Somatic Complaints

Somatic complaints are said to be rare following LSD ingestion, and when they do occur do not preferentially involve any particular organ system.[19,55] At first glance, therefore, the relative frequency of such complaints among those individuals reporting adverse effects from LSD (18 of 76,

or 24%) seems striking. However, somatic complaints occurred in only 7 of the 50 cases within the "probable" LSD *effect category* compared with 11 of the 26 cases in the "possible," "doubtful," or "no LSD" categories. Somatic complaints are over-represented in these latter categories not only because they were somatic--and therefore atypical of LSD--but also because in most cases the time of onset was more than 2 years from the time of LSD exposure or the symptoms were clearly attributable to other causes (e.g., the subject complaining of shortness of breath had a 35 pack/year history of cigarette smoking and managed a cabinet shop so that he was constantly exposed to volatile hydrocarbons). It should also be noted that virtually all of the somatic complaints reported have been demonstrated to occur commonly in healthy subjects who have received no medication.[69]

In three cases within the "probable" effect category the complaints *attributed to LSD were exclusively* somatic. In the first case, the subject began to experience headaches immediately after LSD exposure. These continued on almost a daily basis for the next 6 months, after which they completely disappeared. In the second case, the subject experienced a 3- to 4-week period of "nervous exhaustion" 1 year after LSD testing. In the third case, the subject experienced sexual impotence for 1 to 4 weeks following each of three LSD exposures. For the other categories, the exclusively somatic complaints as well as the length of time from LSD exposure to onset were as follows: "problems with nervous system" and muscle spasms (16 years); "eyes dilate a lot" (?); generalized weakness (11 years);

chronic shortness of breath (reported from time of LSD ingestion forward); stiff muscles and hot flashes (?); photophobia (reported from time of LSD ingestion forward); and allergies (2 years). Two subjects who did not receive LSD specifically presented somatic complaints. One experienced recurrent headaches from the time of chemical agent exposure through the next 2 years; one has experienced recurrent dizziness over the past few years. These latter symptoms are believed to be due to inner ear dysfunction but are reminiscent of the sensations experienced during chemical warfare experimentation.

For subjects with both somatic and psychological complaints, headache was the most common complaint, occurring in three cases. Other complaints included fatigue, tinnitus, paresthesias, chronic gastric distress and, in one remarkable case, a combination of blurred vision, headache, chest pain, bad cough, "hard breathing with sinus congestion," and "doesn't always hear."

C. Depression

Depression is probably the most commonly reported prolonged reaction to LSD among normal research subjects.[37] Generally, it is self-limited and results in little serious disability. In the present study, 12 subjects reported depression as a possible complication of their LSD exposure. These constitute 4 per cent of the total group examined and 16 per cent of those subjects reporting adverse effects resulting from LSD. The reported episodes of depression lasted from a few days to

several years. Psychiatric intervention or hospitalization, or both, was required in 6 of the 12 cases.

The most serious potential outcome of depression is suicide. The frequency of suicide related to LSD is usually given as approximately one per thousand individuals exposed. This figure is based largely on Cohen's 1960 survey of 62 physicians using LSD either for psychotherapy or for experimental research. Forty-four physicians replied giving information on approximately 5,000 persons receiving LSD or mescaline. In the total patient group there were nine suicide attempts of which four were successful. All attempts for which the time frame was given were made within 6 months of LSD exposure. Commenting on these figures, Hoffer[37] stated that "considering that LSD has usually been given to the most hopeless psychiatric cases including addicts, alcoholics, psychopaths, and others, this is a remarkably low figure." Although Cohen's findings were later challenged on the basis of missing information from 18 of the 62 physicians queried, as well as the relatively short length of follow-up, a more recent survey of 4,300 treated subjects of the British Isles produced a very similar suicide rate of 0.7 per thousand.[51] In the present series, there was one definite suicide and one death occurring in circumstances which raised the possibility of suicide. In these cases, periods of 3 and 15 years had elapsed between LSD exposure and death--making any relationship between the two events difficult to establish.

Among the subjects examined, there was one unsuccessful suicide attempt. This individual became profoundly depressed 2 years after

participation in LSD experiments and attempted to commit suicide by slashing his wrists. With brief hospitalization and psychotherapy, this subject made a complete recovery and has remained asymptomatic. In this case, the time elapsed between LSD exposure and the onset of depression--2 years--is somewhat longer than has been typically reported for LSD-triggered suicide attempts, and the relationship, while somewhat more suggestive than in the preceding case, remains uncertain. A second subject made a suicide gesture. This individual developed recurrent episodes of severe depression subsequent to LSD exposure in 1967. In 1971 he was contemplating jumping off a bridge but was readily dissuaded by a passer-by. After a brief hospitalization the subject completely recovered and has remained asymptomatic.

Suicidal ideation unaccompanied by suicide attempt was reported by two subjects. In the first case, however, the historical progression of symptoms was somewhat convoluted. This subject received LSD in 1967. A few months later he was transferred to Vietnam where he participated in combat. While in Vietnam he underwent a reported "personality change" becoming increasingly irritable and restless. However, under the circumstances, this was not entirely unexpected or uncommon. Two years later, after returning to the United States, he experienced a brief hallucinatory episode. At about the same time he began experiencing marital difficulties attributed to his "personality change." Six years later he became separated from his wife and developed severe depression, suicidal thoughts, and auditory and visual hallucinations. However, these last phenomena

were not similar in nature to the preceptual distortions experienced under LSD follow-up. This subject was placed under psychiatric treatment when this history was obtained. In the second case, the subject suddenly became intensely depressed, stopped his car by the side of the road and wandered into nearby woods for about 40 minutes with vague suicidal thoughts. After this episode, the subject's depression resolved and he has remained asymptomatic. A third subject also reported marital disruption and, in addition, serious financial irresponsibility because of depression following LSD exposure. However, in this case suicidal ideation was denied.

Of the seven remaining subjects reporting depression, the depressive symptoms began immediately after the LSD exposure and lasted several days, 6 months, and 12 months before resolving spontaneously. Paradoxically, the subject whose depression lasted only a few days developed episodes of paranoid and grandiose ideation 12 months later.

D. Personality Change

Both transient and long-term personality changes are frequently reported following LSD ingestion.[11,19,27,55,57,72,74] Changes in a positive direction--improved self-awareness, more tolerance, less anxiety, less defensiveness--are usually the intended goals of the use of LSD in psychotherapy. In the present study, most of the reported personality changes were generally more negative in character. Subjects reported social withdrawal, loss of interest in work, irritability, and

aggressiveness. Since most of the reports of favorable personality changes come from circumstances specifically designed to enhance the production of these effects, part of the difference noted in this study may be attributable to the setting (i.e., military chemical warfare experiments) in which the LSD was given. It should also be noted that adverse personality changes were reported both by "pure" LSD recipients and by subjects who received both LSD and other drugs, as well as by one subject who may not have received any drugs at all. Unfortunately, very few of the records from the initial pre-LSD psychological examinations have apparently survived to the present so that they have not been available for review and comparison with the present results.

Two subjects reported relatively positive changes. One reported changes similar to those mentioned above (i.e., improved self-awareness, more tolerance, etc.) and one reported an inclination to take life more seriously after LSD exposure.

Among the more alarming possible personality changes reported was a trend toward increased irritability and violent outbursts. Homicide and attempted homicide as well as other assaultive behavior are rare but not unheard of following LSD ingestion.[7,44,75] None of the patients reporting increased irritability and temper outbursts did any significant physical harm to others; however, in some cases considerable family disruption resulted. Similar negative personality changes have been reported by Cohen and Ditman (1963) and by Ungerleider, et al (1966).

In two cases, individuals reported episodic social withdrawal and moodiness. However, in neither case were these changes persistent enough to be categorized as personality changes. In one case, these episodes tended to be triggered by alcohol and in one case by recurrent fear of having "revealed secrets." (See below.)

E. Anxiety

Another frequently reported symptom following LSD ingestion was anxiety (n=6). Subjects reported both sporadic recurrent anxiety episodes, often triggered by stress, as well as prolonged constant increases in anxiety levels. LSD exposure is reported to be particularly anxiety provoking in individuals with rigid, tightly controlled personalities for whom actual or threatened loss of self-control is a severe stress.[55,57] Occasionally, post-LSD anxiety is severe enough to be the presenting diagnosis for psychiatric admission.[35,84] For two individuals in the present study, episodic anxiety was the only reported complication of LSD ingestion. The remaining subjects experienced both anxiety and other symptoms such as flashbacks, depression, and various somatic complaints. In no case was the degree of anxiety sufficient to lead to hospitalization.

F. Nightmares

Probably closely related to underlying anxiety, increased nightmares were reported by five subjects including two in which nightmares were the sole LSD-related complaint. The LSD literature rarely mentions nightmares

specifically. However, there is no reason to assume that they are not common sequelae of LSD exposure. It may be of some theoretical interest that only one subject reported both nightmares and flashbacks inasmuch as flashbacks often resemble the intrusion of nightmare-like material into waking consciousness. Nightmares were reported by four "pure LSD" subjects and one subject who is not known to have received any drugs.

G. Paranoia

Paranoid ideation, like anxiety, is not infrequently reported following LSD ingestion.[19] Four subjects in this study reported paranoid ideation among the problems they attributed to LSD. The most severe example was that of a subject who was hospitalized for 1 week with a diagnosis of acute paranoid state. This hospitalization occurred 1 year after the subject's presumed participation in chemical warfare experiments. Available records, however, indicate that he received no drugs although he was at Edgewood Arsenal. The remaining three subjects received LSD exclusively. Two reported recurrent suspicious feelings and social withdrawal associated in one case with alcohol ingestion. The other subject apparently received LSD under test conditions requiring that he attempt to resist efforts at interrogation by the experimenters. This subject subsequently developed considerable underlying anxiety about his self-worth, and 1 year following the experiments he began to experience a series of episodes--often precipitated by alcohol--in which he felt that he was a "super spy" who had to carefully guard important secrets. These episodes continued intermittently for several years before resolving completely.

H. Dissociative Episodes

A particularly interesting finding among the LSD subjects was the occurrence of dissociative episodes (n=5). Hysterical neurosis, dissociative type, may include any of the following symptoms: amnesia, somnambulism, fugue, and multiple personality. For the five subjects in this study, the reported episodes frequently resembled fugue states in which the individual carries out complex activity, often including traveling considerable distances, only to "awaken" suddenly and find that he can neither recall nor explain his prior activity. For two subjects the dissociative episodes occurred exclusively within the first few days of LSD ingestion. For one, the dissociative episodes began the first year after exposure and recurred intermittently for the next 7 years. For the remaining two subjects, the episodes began at much later dates. For at least three of the five subjects, the dissociative episodes seem to have been triggered by, or at least associated with, alcohol ingestion. Although acute panic states, dissociative delirium, and transient confusional states have all been reported following LSD ingestion, and not infrequently triggered by alcohol,[24,72] descriptions of classical fugue states following LSD are very rare. Fortunately, none of the subjects exhibiting fugue symptoms was injured or the cause of injury to others. However, one subject believes his dissociative episodes, along with other problems, caused his reduction in rank while in the service, work-related problems as a civilian, and considerable marital disruption leading eventually to divorce.

I. Phobic Neurosis

Another condition which is rarely discussed in connection with LSD exposure is phobic neurosis. Two subjects developed severe phobias following chemical warfare testing. The first, who received both LSD and other agents, developed a snake phobia, apparently as the result of terrifying hallucinations of snakes while under the influence of a psychoactive agent and subsequent recurrent nightmares concerning snakes. The second, who is not known to have received any drugs, stated that while hallucinating from "LSD" he was handed a salt shaker. He became terrified of the salt shaker and following the experiments developed a generalized fear of salt shakers. In both cases, the symptoms have persisted to the present time although they have markedly diminished in severity.

J. Memory Loss

Four subjects reported non-specific memory loss but in two cases the symptoms were of very recent onset and are more likely to be due to the normal aging process than to LSD ingestion 21 years ago (both received LSD in 1958). The third subject's complaints of memory loss were not specific as to onset and severity. For the fourth subject, the memory loss appeared to refer to transient confusion associated with probable flashbacks.

K. Illicit Drug Use

LSD is not physically addicting and probably not psychologically habituating given the frequent observation that many LSD users decrease

and discontinue their use of the drug over a period of time.[55] LSD usage has never been conclusively shown to lead to the abuse of other illicit substances. In the present study two subjects reported the use of other illicit drugs--heroin in one and multiple hallucinogens in the other--following LSD exposure. The heroin addict stated that his LSD experience led to a "desire to experiment" with other drugs, but he did not first use heroin until after discharge from the Army 2 years after his LSD exposure. The polydrug abuser reported experimenting with other hallucinogens as a result of LSD exposure but psychiatric evaluation uncovered a long history of social maladjustment extending into childhood. The abuse of alcohol following LSD has already been considered.

L. Psychosis

Conspicuous by its absence from the list of adverse reactions to LSD was prolonged psychosis. This was by far (63%) the most common adverse reaction in the survey by Smart and Bateman[75] and is estimated by Cohen (1960) to occur in 0.8 per 1,000 experimental subjects given LSD. Although the prolonged psychotic state can begin immediately after LSD ingestion, Hatrick and Deshurst[35] reported two cases in which prolonged psychosis began 2 weeks and 2 months, respectively, after LSD ingestion. In the present study one subject was hospitalized with a diagnosis of acute paranoid state 1 year after LSD ingestion. His symptoms resolved with tranquilizer medications and he was discharged 1 week after admission. Both the time of onset and the rapidity with which the symptoms resolved are highly unlike the psychotic reactions to LSD. Moreover, this subject who is not

known to have received any chemical warfare agents reported a 2-week long period of "confusion" occurring some time after his return to his normal duty station. The details of this episode are vague and since hospitalization was not required it seems questionable that the symptoms were overtly psychotic.

Present Complaints

A relatively large proportion of those LSD subjects who reported adverse effects from LSD exposure also reported either persistence of some or all of their symptoms to the present time or the recent onset of their symptoms. Forty-one subjects (54% of those with complaints and 13% of the total group) reported present problems but 22 of these fell within the "possible," "doubtful," or "no LSD" categories. Somatic complaints in particular were over-represented in this group. Of the "probable" LSD effects which have persisted to the present--exclusive of flashbacks which have already been mentioned--personality changes and recurrent depression were the most commonly mentioned. (See Table 41.)

Disability Resulting from LSD Exposure

Taken as a group, those subjects examined or otherwise evaluated by the LSD follow-up seem to have suffered remarkably little disability. Based upon the demographic data obtained, the group in general demonstrated marital stability, exceptional levels of education and employment, and no more medical or psychiatric illness than might have been expected

for a random sample of the population. Even for the subjects with specific LSD-related complaints, the resultant disability, if any, was generally mild and transient.

Some subjects, however, experienced more significant socioeconomic difficulty. Marital and family disruption resulting from reported personality changes, depression, alcohol abuse, etc., were reported by seven subjects (2%), two of whom became divorced. Eleven subjects (3.5%) reported obtaining psychiatric treatment for LSD-related problems and six of these required one or more hospitalizations. At least five (1.5%) subjects experienced work-related difficulties and job instability which they attributed to LSD exposure. In some of the above cases, however, the reported difficulties were clearly associated with either alcohol or drug abuse and, as has been seen, there is little evidence that LSD exposure *leads directly to either. Including these latter cases, a total of 23* subjects (7% of the total group) felt that symptoms related to prior LSD exposure had significantly compromised, at least temporarily, their socioeconomic adjustment. Significant socioeconomic problems are not uncommon in the general population. A subgroup of 7 per cent with such history in the total group of LSD recipients is perhaps not too different than one might anticipate in the general population.

SUMMARY OF FINDINGS AND OBSERVATIONS

In response to widespread concern about the occurrence of prolonged *adverse effects in former volunteer participants in chemical warfare*

experiments using LSD, the Army has carried out a series of follow-up examinations extending from 1974 through 1979. The initial volunteer population was thought to number 741 individuals. At the conclusion of the follow-up period, 320 subjects had been evaluated and the remaining 421 potential subjects had been determined to be deceased, unlocatable, uninterested in receiving examination or otherwise providing information, or already evaluated by another branch of the military service. For both theoretical and practical reasons it proved impossible to obtain a matched control group with which to compare LSD subjects. Furthermore, available records indicated that 37 per cent of the follow-up subjects received other chemical warfare agents, including many potent psychoactive drugs, and 12.5 per cent of those evaluated could not be shown to have definitely received LSD although their names had appeared on the "LSD roster." Despite these serious shortcomings which precluded using standard statistical methods to establish cause/effect relationships, a clinical survey of the subjects was undertaken. As a group, the "LSD subjects" appeared to be relatively stable socially, unusually well educated, and economically successful. The medical and psychiatric findings for those 220 subjects examined directly, as well as that obtained from the additional 100 subjects examined by questionnaire, appeared to generally parallel both in type and frequency the findings which could be expected to be found in a comparable segment of the general male population. Specific concerns about the provocation of seizure disorders appeared to be unfounded. Except for the question of a possible increase in congenital heart disease,

there was no strong evidence of LSD-related abnormalities in offspring. There was an apparent increase in abnormalities found on administration of the Halstead-Reitan Neuropsychological Test Battery. However, a possible etiology--other than LSD or other chemical warfare agents--was found in 56 of the 77 cases reported as showing some degree of impairment. The reported abnormalities were not characteristically limited to any portion of the battery but were scattered throughout making a single specific etiology unlikely. Seventy-six subjects (24%) reported symptoms which they perceived as being related to their LSD exposure 10 to 20 years earlier. Of these, 50 (16%) reported symptoms which both occurred within reasonable proximity (2 years) to LSD exposure and were similar to known LSD effects. Flashbacks were the most frequently reported complaints, and although no more frequent than in other studies (about 8%), they were unusually persistent. Depression, personality change, and anxiety were also frequent complaints. Somatic complaints were often reported but only occasionally occurred within reasonable proximity of LSD exposure. Other complaints--such as nightmares, dissociative episodes, paranoia, episodic social withdrawal, and memory loss--were reported but were less frequent. Although 11 patients reported that they required some psychiatric intervention with reference to LSD-related complaints, the amount of significant socioeconomic disability attributed to LSD for the study group as a whole was small (approximately 7%).

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Table 1. Final Status of the 741 Subjects Listed on the "LSD" Computer Roster

320	evaluated	
	220	in-patient or other direct examinations
	100	evaluated by questionnaire
193	unlocatable	
24	deceased prior to follow-up	
149	locatable but no information available	
55	USAF personnel followed separately	
741	total	

Table 2. Sites of Examination

WRAMC		171
LAMC		22
DDEAMC		27
	total	220

Table 3. Examinations by Project Designation

Project 33	(1974-5)	19
Project 28	(1975-6)	23
Project 50/50	(1977)	68
Main Follow-up	(1978)	110
	total	220

Table 4. Demographic Data (Age, Marital Status, Military Status) of 320 Subjects

Age	
Mean	45 years
Median	44 years
Range	30 - 72 years
Marital Status	
Married (first marriage)	234
Married (multiple)	27
Separated	14
Divorced	12
Single	33
total	320
Military Status	
Active duty	37
Retired military	117
Civilian	158
Unknown	8
total	320
Military rank at time of chemical warfare experiments	
Officer	110
Enlisted	203
Unknown	7
total	320

Table 5. Demographic Data (Level of Education, Employment) of 320 Subjects

Years of formal education	
less than 12 years	10
12 years	68
12 - 15 years	79
16 years	56
more than 16 years	90
unknown	17
total	320
Level of employment	
Professional	67
Managerial	51
Public Service	50
Small business	23
Sales	25
Skilled labor	56
Unskilled labor	5
Other or unknown	43
total	320
Current employment status	
Fully employed	272
Part-time	3
Retired	27
Unemployed	10
Unknown	8
total	320

Table 6. Sites of LSD Exposure

Edgewood Arsenal	180
Fort McClellan	68
Fort Benning	28
Fort Bragg	40
Dugway Proving Ground	3
Unknown	1
	320

Table 7. Number of LSD Exposures per Subject

Number of Exposures	Number of Subjects
0	39
1	175
2	43
3	12
4	1
5	2
Unknown	48
Total	320

Table 8. Number of Non-LSD Exposures per Subject

Number of Exposures	Number of Subjects
0	203
1	51
2	38
3	13
4	9
5	1
6	5
Total	320

Table 9. Specific Other Agents Administered to 320 Subjects

		Number of Subjects
Anticholinesterase		
301060	Classified	2
EA 3443	Classified	1
[illegible]	[illegible]	[illegible]
CS 27349	Benzilate, 2a - tropanyl, hydrochloride	1
DITRAN		1
BZ	Benzilate, 3 quinuclidinyl	12
SCOPOLAMINE		18
Anticholinesterase		
Unspecified		2
GD	Soman	1
VX	o-ethyl S-(2 - diisoprophylaminoethyl) methyl phosphonothioate	22
G-VAGT	G or V agent	5
Antidotes		
Atropine		12
THA	Tacrine or tetrahydroaminoacridine	1
Oximes		
PAM	Pralidoxime	9
Riot Control		
T792	CS	3
DM	Adamsite	3
CS	o-chlorobenzylidene malononitrile	9
Miscellaneous Incapacitants		
EA 2233	Acatate,[3-(1,2 -dimethylheptyl)-7,8,9 10-tetrahydro-6,6,9-trimethyl -6H-dibenzo [b,d]pyranyl]	13
EA 1476	6H-Dibenzo[b,d] pryan-1-ol, 3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl	3
ALD	Acetyl lysergic acid diethylamide	1
302089	1,3,8-Triazaspiro [4,5] decan -4-one, 8-[-3(p-fluorobenzoyl)-propyl]-3-methyl-1-phenyl, hydrochloride	
BOL	Brom-lysergic acid diethylamide	4
Miscellaneous		
Alcohol		1
5HTP	5-hydroxy tryptamine	4
Heparin		1
Saline		1
Propylene glycol		1
Unknown		31
Other		35